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ANEMIA IN TRAUMATIC BRAIN INJURY: WHEN TO TRANSFUSE?

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Anemia in Traumatic Brain Injury: when to transfuse?

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Para a minha avó, pelo apoio e amor incondicional,

Para a minha mãe, por me ter ensinado a ser melhor pessoa,

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Para os meus irmãos, pela ajuda em todos os momentos,

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ANEMIA IN TRAUMATIC BRAIN INJURY: WHEN TO TRANSFUSE?

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Abstract

Purpose of review: Patients with traumatic brain injury (TBI) are typically multiple trauma patients, presenting with various pathological entities that jeopardize their survival. Anemia is one of the most common abnormalities in trauma patients, and is considered a worse prognosis determinant. However, strong recommendations, and high-quality prospective studies to support the best transfusion practices in brain trauma patients are scarce, if not inexistent, leading to major doubts in optimal treatments. This review's intention is to summarized actual evidence regarding this issue, mainly the hemoglobin thresholds and other important triggers used in treating anemic TBI patients.

Recent findings: In general, in intensive and in neurocritical care, a restrictive transfusion method has been proven safe and, at least, not inferior to previously advocated liberal thresholds. Nevertheless, other physiological variables have been recently studied in treating anemia in this patients' population, leading to more liberal approaches in red blood cell transfusions, due to recent implemented "triggers". Allowing a normal oxygen delivery and achieving an optimal brain oxygenation is dependent of multiple factors, independent of hemoglobin concentrations.

Summary: Nowadays, there is no sufficiently high-quality information to provide strong general recommendations in managing anemia in traumatic brain injury. Transfusions are one of the main options, but they have both benefits and risks that must be taken in account in every single case.

Keywords: Red blood cell transfusions, anemia, traumatic brain injury, brain oxygenation, intensive care, hemoglobin

Introduction

Anemia in adult patients is defined by a blood hemoglobin concentration below 12 g/dL (women) or below 13 g/dL (men), and can be classified in severity as mild (11-11,9 g/dL for women, 11-12,9 g/dL for men), moderate (8-10,9 g/dL, for both genders), or severe (below 8 g/dL, for both genders) [1].

Traumatic Brain Injury (TBI) is one of the major causes for admission in the Neurocritical Care Unit (NCCU), being responsible for approximately 30% of all injury-related deaths in the United States [2].

Anemia develops in at up to half of all TBI patients, and is a risk factor for secondary brain damage and, therefore, worse prognosis [3].

As transfusion of red blood cell units is considered a vital tool for early resuscitation of anemic patients in critical situations [4], studies have been conducted regarding which should be the most appropriate threshold, mainly based in hemoglobin concentrations, for transfusion in ICU and, specifically, in TBI patients, with controversial results.

Due to the lack of strong evidence-based recommendations for transfusion practices in TBI patients, mainly to the very few randomized controlled trials conducted on this problem, and the inconsistency in results from previous low-quality studies, practicians are not able to treat this patients' population in a secure and accurate manner.

Methods

Using the terms "anemia", "traumatic brain injury" and "blood transfusion" in the database PUBMED, articles were selected and included in this review, based on their relevance and adequacy towards the subject.

Discussion

Epidemiology of TBI

In 2010, TBI caused almost 2.5 million emergency department (ED) visits, hospitalizations, or deaths, representing an increase of ED visits due to TBI by 70%, while hospitalization and death rates only increased by 11% and 7%, respectively. The direct and indirect costs associated with this clinical entity are more than substantial [5].

In 2017, the Center for Disease Control published a report on TBI [6], where they stated that most injuries resulting in TBI lead to emergency department' visits (ED), while hospitalizations and deaths occurred in a minority of cases. Of all the emergency department' visits, hospitalizations and deaths registered in the United States in 2013, only 1,9% were due to TBI, the equivalent of one in every 50 ED visits, and 2,2% of all deaths.

When analyzed by age groups, TBI's diagnosis was more common in extreme ages, such as elderly people older than 75 years, infants (0-4 years) and young adults (15-24 years). The same happened in ED visits, where young adults were the main contributing age group (17,9% of all TBI-related ED visits). However, hospitalizations and deaths were more frequent only the oldest age groups (≥65 years), especially in those older than 75 years (31,4%, and 26,5% of hospitalizations and deaths related to TBI, respectively).

Falls (47,2%), object collisions (15,4%) and motor accidents (13,7%) were the most common mechanisms of injury. Falls happened more frequently in very young (0-4 years) and elderly individuals (≥65 years), whereas object collisions and motor accidents typically occurred in children and adults (0-24 years, and 15-44 years, respectively). TBI was also more frequent in men than women (1,14 times more common), except for the cases of falls as the mechanism of injury [6].

Affecting 2% of the USA's population every year, TBI is an important pathological entity, with significant mortality and morbidity. Each case can vary from mild concussions which only require surveillance, to large hemorrhages that need urgent surgical interventions (such as evacuation of hematomas) [7]. Despite the technological advances in the field of intensive care and neuromonitoring, 20% of patients die, and 35% of the survivors suffer with debilitating neurological deficits [8].

Oxygen and Blood Supply to the Brain

As in every other organ in the human body, the oxygen delivery (DO_2) to the brain tissues depends on the cardiac output (CO), which determines the cerebral blood flow (CBF), and the arterial content of oxygen (CaO_2).

At the same time, CO depends on the stroke volume (SV) and heart rate (HR), whereas CaO_2 depends mostly on the hemoglobin concentration (Hb) and its rate of saturation with oxygen (SaO_2%), with a minor contribution from oxygen dissolved in the blood (PaO_2). The equations supporting the physiology of oxygen delivery are the following:

$$DO2\ (mL\ O2/min)\ =\ CBF\ (L/min)\ x\ CaO2\ (mL\ O2/L)$$

$$CBF\ (L/min)\ =\ SV\ (L/contraction)\ x\ HR\ (contractions/minute)$$

$$CaO2\ =\ [1{,}39\ x\ Hb\ (g/L)\ x\ SaO2\ (\%)]\ +\ [0.003\ x\ PaO2\ (mm\ Hg)]$$

The flow of blood through the brain's microcirculation is also dependent of other variables, including the radius of the vessel (r), the differential of pressures between two areas (ΔP), the blood's viscosity (η), and the vessel's length (L). ΔP can be represented in the cerebral system by the cerebral perfusion pressure (CPP). The Hagen-Poiseuille equation demonstrates the relation between all the variables presented:

$$Flow = \frac{\pi \; x \; r4 \; x \; CPP}{8 \; x \; \eta \; x \; L}$$

By analyzing this equation, it can be inferred that vasodilation (increase of the radius of the vessel) and increase of CPP lead to higher blood flow to the brain, while a increase in viscosity (**η**), as in dehydration states or after a red blood cell transfusion (RBCT), leads to the opposite effect. Also, it is important to highlight that, due to the fourth power inputted on the radius of the vessel, small changes in vessel's diameter can lead to grand variations in the CBF.

In order to determine if CBF is enough to allow sufficient or even normal brain oxygenation, intensivists calculate the CPP, using the formula:

$$CPP \; (mmHg) \; = \; MAP - \; ICP$$

MAP is the Mean Arterial Pressure, easily measurable with manual or automatic sphygmomanometer, and ICP is the Intracranial Pressure, measured through intracranial probes, with normal values being 7-15 mmHg, and values above 20-25 mmHg needing medical intervention. A raise on MAP leads to higher CPP levels, which can aggravate preexistent cerebral edema, while elevation of ICP (such as in TBI) reduces CPP, with subsequent risk of ischemia.

The Effects of Anemia in the Brain's Physiology

The human brain is one of the organs with the highest oxygen extraction rate (OER) and consumption of oxygen (VO_2) for its basic metabolic necessities. The oxygen being continuously delivered to the brain by the cardiovascular system is mostly absorbed and utilized in the production of energy.

Anemia, due to the decrease in hemoglobin concentrations, leads to a major decrease in the CaO_2 and the oxygen delivered to the brain. This results in inadequate DO_2, incapable of meeting the cerebral metabolic rate for oxygen consumption ($CMRO_2$), leading to tissue ischemia. $CMRO_2$ can be determined by the following equation, where $AVDO_2$ is the arterial-jugular oxygen content difference:

$$CMRO2\ (mL/min/100g)\ = \frac{AVDO2\ x\ CBF}{100}$$

In acute anemia states, as a countermeasure, CBF is preferentially raised, compared to the flow to other lesser vital organs [9], through various compensatory mechanisms, as shown in experimental studies in healthy individuals. These include:

(1) Sympathetic stimulation: carotid and aortic chemoreceptors detect a decrease in the arterial content of oxygen and respond by activating the sympathetic nervous system, resulting in higher blood pressure (systemic vasoconstriction) and cardiac work (elevation of the heart rate and of the left ventricular stroke volume) [10]; also, the upregulation of ß$_2$ receptors in the blood vessels leads to cerebral vasodilation [11]; this guarantees a rise in CBF to counterbalance the lower CaO_2 present in anemia, in order to maintain a proper DO_2.

(2) Anemia itself, due to a lower number and concentration of red blood cells (lower hematocrit), leads to a decrease in blood viscosity, which facilitates blood flow through the cerebral microcirculation [12]; it also increases venous return and reduces systemic vascular resistance, with a resulting additive effect to the improvement of oxygen delivery to the brain [13].

(3) The encephalic cells, namely endothelial cells, perivascular astrocytes and neurons, produce nitric oxide (NO) in response to lower oxygen availability [14], which in turn leads to relaxation of the vascular smooth muscle cells, resulting in dilation of the cerebral vessels, and a substantially higher CBF [15].

(4) In response to a partial or total deficit of oxygen, the brain responds by rising its oxygen extraction rate [16], in order to maintain its metabolic energy production and avoid the use of anaerobiosis, which results in the buildup of lactate, reactive oxygen species and other prejudicial metabolites that can worsen the overall state of the brain's health and jeopardize the patient's survival [11].

(5) In severe anemia, cerebral hypoxia induces the cellular production of HIF (hypoxia-inducible factor), a transcription factor that allows cells to adapt to low-oxygen states, protecting them from ischemia [17]; it also stimulates the renal production of EPO (erythropoietin), a hematopoietic stimulator of the bone marrow, as well as a inhibitor of neuroral apoptosis with neuroprotective effects [18], and the production of VEGF (vascular endothelial growth factor), a angiogenesis stimulator that allows long-term adaptations to hypoxia [19].

(6) Hemoglobin itself functions as a oxygen sensor, stimulating the release of local-acting vasodilators, in response to tissue hypoxia, such as NO (nitric oxide) and ATP (adenosine-5'-triphosphate), increasing regional blood flow, in order to balance the delivery of oxygen with its consumption [20].

Part of this mechanisms are intrinsic to the brain tissue, being commonly reffered to as "cerebral autoregulation", that allow, collectively, the brain's self-adaptation to a wide variations of systemic variables, for instance, the capacity to withheld wide variations of systemic arterial pressure while maintaining a relatively constant CBF [21,22].

Although these mechanisms are effective and allow normalization of cerebral DO2 in anemic patients, there is a critical threshold value for hemoglobin concentration at which the brain's compensatory mechanisms start to fail, estimated at 5-6 g/dL [12] . After this point is reached, maximum vasodilation and CBF values are reached, cerebral DO2 starts to diminish, tissue ischemia and hypoxia establish, and changes of the mental status and cognitive deficits start to develop [23].

Red Blood Cell Transfusion (RBCT) in Critical Care

In critical care, blood transfusion is still a live-saving procedure and its early and aggressive use is essential for resuscitating patients with massive hemorrhages, especially in the context of trauma [4]. Transfusions are used, not only as a initial measure of treatment, but also in the management of critically ill patients who suffer from potentially complicating anemia, reason why at least 50% of these patients receive more than one unit of RBC's during their stay in the ICU [24]. Although the physiological rationale of raising the arterial content of oxygen (CaO2) and, therefore, the DO2 for the body's tissues in risk of ischemia [21], was the argument for a mainly "liberal" use of RBCT , more and more evidence, published and discussed over decades, lead to the conclusion that a more restrictive use of RBCT would likely be equally or even superiorly beneficial for patients, due to the reduction of complications and adverse effects associated with transfusion of blood products ([25],[26]).

In fact, most retrospective studies done on this issue show an association between "liberal" transfusion strategies and negative outcomes, such as higher mortality rates, multi-organ failure [27], nosocomial infections (due to immunosuppression) [28], respiratory and cardiac complications (namely, ARDS) [29], and longer hospital stay [30].

Complications of blood transfusions can be classified as "common" to all blood products, or "specific" of individual blood components. "Common" complications are the majority (85,5% of all report incidents) of transfusion-related complications (85,5% of all report incidents), and are mostly related to errors in administration, such as: ABO-incompatible RBCT; anti-D immunoglobin errors; transfusion of the wrong blood component (IBCT); handling and storage errors; delays in transfusion; over or avoidable administration of blood components; and nonspecific reactions to transfusions (FAHR – Febrile, allergic and hypotensive reactions) [31].

More specific complications are more serious and life-threatening, though possibly preventable. This include: Transfusion-Associated Circulatory Overload (TACO), Haemolytic transfusion reactions (HTR), Transfusion-associated dyspnea (TAD), Transfusion-related acute lung injury (TRALI), Post-transfusion Purpura (PTP), and Transfusion-associated graft-vs-host disease (TAGvHD). In the intensive care unit, the most common, lethal, and difficult to manage situations are TACO, TAD and TRALI, which contribute to 44,1%, 5,9% and 3,7%, respectively, of the 53,7% of transfusion-related deaths due to respiratory complications.

Effects of Anemia in TBI

Anemia is common in intensive care units, affecting up to 70% of critically ill patients [32], and 50% of severe TBI patients [33]. It has been demonstrated a tendency of daily decrease of hemoglobin levels of 0,5 g/dL, while in ICU stay [34].

In neurocritical care patients, the etiology of anemia is multifactorial [35], similarly to other ICU patients populations, with causes including: blood loss, due to hemorrhages or medical procedures (e.g. frequent phlebotomies); myelosuppression, with a consequent decrease in production of hematopoietic cells, and elevated consumption of red blood cells, secondary to systemic inflammation [36]; abnormalities in the EPO and iron metabolisms; hemodilution secondary to intravenous fluid resuscitation and hemorrhages [37].

After initial damage to the brain tissue, changes in the brain's metabolism and autoregulation processes can lead to secondary brain injury, mainly tissue acidosis and ischemia [21], which can be even greater than the primary injury, caused by a multitude of neurocritical entities, including TBI. The existence of so-called "ischemic penumbra" areas, areas of brain tissue between normal and infarcted areas, with mild to moderate ischemia, are of "high-risk", as they are particularly vulnerable to even subtle changes in

the delivery of oxygen and, therefore, must be closely monitored to avoid propagation of irreversible damage [38].

Anemia, hypoxemia and hypotension are systemic, reversible causes of secondary injury, and many other factors contribute to the worsening of this damage, such as: intracranial hypertension, vasospasm (typically after SAH), loss of autoregulation, and the uncoupling of blood flow and metabolic pathways [39].

Anemia is, therefore, less well tolerated by patients with acute neurological stress, such as TBI, as alterations in the oxygen delivery and in oxygen-dependent metabolic pathways, increase the risk for secondary ischemia.

In response to the lack of oxygen availability to produce metabolic energy in the mitochondria, the neuronal cells utilize the pyruvate produced from glucose oxidation in the cytosol, and transformed it into lactate, through the oxygen-independent process of lactic fermentation. This process allows the cells to obtain energy from glucose in anoxic environments, with the downside of endangering their own survival, due to lactic acidosis that can abolish vital cellular mechanisms [40].

Therefore, evaluation of systemic lactate concentrations (through blood samples) and the regional lactate:pyruvate ratio/LPR (through cerebral microdialysis probes), allows practicians to determine the state of the brain's metabolism, and provides information about the risk of neurological dysfunction, in low oxygen states such as anemia [41].

These metabolic measures serve as indirect predictors of the $CMRO_2$.

As so, one prospective study done in 28 severe TBI patients, determined that low hemoglobin levels were related to higher lactate differences, and, therefore, a important predictor of brain ischemia [42]. These differences can be caused by a decrease in CMRO2, where less utilization of oxygen leads to anaerobiosis, as it was shown in a similar prospective study done in 64 acute brain injury patients, undergoing serial ^{133}xenon

studies for monitoring of regional cerebral blood flow and global cerebral oxygen metabolism [43].

Another way of evaluating the effects of anemia in the human brain is by measuring of the brain tissue's partial oxygen pressure, or $P_{bt}O_2$, through invasive probes placed in strategic regions in the cerebral cortex [44]. This innovative tool is being increasingly used in intensive care, as a means of guiding treatment in patients with acute brain injury [45]. It allows practicians to have a proper idea of the actual balance between oxygen delivery and consumption [46], which is altered in these patients due to various pathological entities, such as perivascular edema, cytotoxic cell swelling, arteriovenous shunting and microvascular collapse [47].

$P_{bt}O_2$ is considered normal for values between 25 and 30 mmHg [45], and its reduction presents a stronger correlation with deficits in oxygen diffusion through the blood-brain barrier and throughout cerebral tissue [48], than it presents with decreased oxygen delivery. In neurocritical care, the minimum goal value for $P_{bt}O_2$ is 20 mmHg [49], has prognosis worsens in lower levels, with 10 mmHg being considered the critical threshold, as it is associated with irreversible neuronal damage and poor outcomes [45].

In TBI, anemia is not always associated to low $P_{bt}O_2$ [50]. Nevertheless, one experimental study conducted in 80 severe TBI patients, found that patients with anemia (<9g/dL) and concomitant low $P_{bt}O_2$ (<20 mmHg) had significant worse neurological outcomes, independently of injury severity, while isolated anemia patients did not [51].

Although a large body of evidence exists, regarding the effects of anemia in healthy patients, these data cannot be interpreted in the same way, when referring to TBI patients. The studies conducted in healthy individuals used lower controlled levels of hemoglobin [52], and this patients had an higher "cerebrovascular reserve", defined as the ability of the

brain's vascular system to respond to different stimuli via vasodilation, when compared to brain-injured patients [53], who are also at a higher risk of developing conditions, such as hemodynamic instability, that can jeopardize their compensatory mechanisms [54].

In TBI, anemia has been inconsistently associated with worse outcomes. This variance in results is believed to be related to different endpoints, outcome measures and cut-off points used, as well as the uncertainty surrounding the actual clinical effect produced by significant changes in outcomes.

Also, sometimes, significant correlations between anemia and mortality or poor neurological outcomes, become non-significant, after taking in account other disease-related variables, as in a retrospective study by Carlson *et al.* [55], where, while studying outcomes in 169 severe TBI patients, correction for disease severity and other predictors of adverse outcomes transformed a significant association between anemia and mortality into a non-significant one.

Nevertheless, most studies show that anemia, either present at baseline and/or during stay in the ICU, is a risk factor for mortality and other adverse outcomes. 2 large studies (CRASH trial [56] and IMPACT study [57]) found that lower admission Hb levels were associated with worse outcome, especially for levels lower than 9 g/dL, which were also associated with metabolic distress in previous brain physiological studies [58]. On the other hand, one review showed that a baseline Hb < 10g/dL was a not a risk factor for mortality[59].

Also, it is considered that repeated measures of hemoglobin levels are more valuable than baseline levels, for the prediction of worse outcomes. In fact, development of anemia in the ICU (Hb < 9g/dL) [60], a mean Hb < 9 g/dL in the first seven days of admission [33], and a higher number of days with hematocrit < 30% [61], have all been associated with worse outcomes, in TBI patients.

Effects of RBCT in TBI

As mentioned beforehand, red blood cell transfusion is considered a life-saving procedure in critical care, due to its immediate effect of raising hemoglobin levels and, therefore, allowing the tissues' metabolic needs to be met [58]. However, data relating to RBCT and its effect in traumatic brain injury patients is limited and rather conflicting, mainly due to the methodological limitations of the studies conducted, such as their mostly retrospective nature, small sample sizes, and variation in outcome measures, that make the generalization of results to this patients' population not viable nor scientifically correct. Therefore, several questions have been raised about the effects of RBCT in TBI:

(1) What is the effect of RBCT in the brain's oxygenation?

By continuously measuring the $P_{bt}O_2$ in brain-injury patients, it has been showed that higher hemoglobin concentrations are linked to higher levels of $P_{bt}O_2$, and one observational study, conducted in 35 brain-injured patients, showed a mean increase in brain oxygenation by 49%, after RCBT [62], independent of changes in CPP. These post-transfusion increments of $P_{bt}O_2$ were also documented in the majority of TBI patients (75%), and associated with a significant increase of Hb concentrations and lower baseline cerebral oxygenation [63]. On the other hand, some studies have showed a decrease in brain oxygenation in up to 33% of such patients [70]–[72].

Together with $P_{bt}O_2$, measuring the jugular venous oxygen saturation, or $SjvO_2$, is one of the methods used for analyzing blood oxygenation after RBCT. One prospective study, in which post-transfusion $SjvO_2$ was measured in 59 cases of severe TBI, showed a significant increase in $SjvO_2$ after RBCT ($p = 0.02$), demonstrating the effect of RBCT in raising systemic oxygen delivery [66].

Another factor that influences changes in brain oxygenation is the autoregulatory mechanisms of the brain itself. Autoregulation can be indirectly evaluated by calculating

the Pressure Reactivity Index, or PRx, a correlation coefficient between MAP (mean arterial pressure) and ICP (intra-cranial pressure) [67]. Its values vary from -1 and +1, with positive values linked to impaired or absence of autoregulation, and, conversely, negative values indicating preserved autoregulation, which is associated with an improvement in $P_{bt}O_2$ [68].

An retrospective analysis, where 28 severe TBI patients were sub-divided in 2 groups based on their mean pre-transfusion $P_{bt}O_2$, showed that patients with higher brain oxygenation previous to RBCT ($P_{bt}O_2 > 20$ mmHg) had a significant increase in PRx, suggesting loss of autoregulation after transfusion, probably because they were not ischemic at baseline, or were in an oxygen-dependent state prior to transfusion. On the other hand, patients with pre-transfusion cerebral hypoxia ($P_{bt}O_2 < 20$ mmHg) had no significant changes in their PRx, equivalent to no changes in autoregulation, suggesting that RBCT does not deteriorate autoregulation in patients who already suffer from hypoxia. Despite major limitations, mainly the small sample size included, this study enlightens some of the doubt surrounding the effects of RBCT in TBI, as we can infer that patients with cerebral hypoxia are better candidates to transfusion, as they do not suffer from post-transfusion impaired cerebrovascular reactivity, and present significant improvements in cerebral oxygenation [69].

NIRS, or near-infrared spectroscopy, is a technology used for brain monitoring since 1985 [70], and it allows intensivists to monitor the regional cerebral hemoglobin oxygen saturation (rSO_2), a measure of the brain's oxygenation status, with the minimum being set to 75% [71], as lower levels are associated to higher mortality and complication rates [72]. One prospective study of 24 severe TBI patients used non-invasive monitoring of rSO_2, using NIRS with bilateral frontal scalp probes, in order to assess this technology's applicability in neurocritical patients subjected to RBCT, as well as to determine the correlation between rSO_2 and other relevant physiological variables. 20 transfusions were

performed in 19 patients, 5 patients' recordings were excluded due to poor signal quality. Hemoglobin concentrations increased significantly after transfusion, and rSO_2 increased in most patients (87% and 81% for right- and left-side lobes, respectively), although this change did not occur in an significant manner, even after adjusting for potential confounders (p = 0,11 and p = 0,68, for right- and left-side lobes, respectively). No statistically significant correlations were found between changes in rSO_2 and changes in other physiological variables. When measuring FTOE (fractional tissue oxygen extraction), they found higher post-transfusion FTOE in patients with lower pre-transfusion Hb levels (Hb < 7g/dL), although this variation was not statistically significant. Also, FTOE decreased after transfusion, but also in a non-significant manner. Being the first study to assess changes in rSO_2 after RBCT in TBI patients using NIRS technology, the authors attributed these non-significant changes in rSO_2 to pre-transfusion Hb levels not being low enough, or changes in Hb levels not being large enough to impact rSO_2 significantly. Also, as cerebral autoregulation was not evaluated, they hypothesized impairment or loss of cerebral autoregulation to be the cause of such non-significant variations. Nevertheless, this novel method as several advantages over other neuro-monitoring methods (non-invasive, easy to use, minimal variability between operators), and takes in account a broader collecting of data from the brain's cortex, allowing to evaluate both regional and global cerebral oxygenation. Therefore, NIRS measurement of rSO_2 should be included in the decision process of transfusing TBI patients [73].

Although a increase in tissue oxygenation has been showed after RBCT, it does not necessarily translate in a higher consumption and utilization of oxygen.

For instance, PET imaging in aSAH patients [74], has shown that transfusions lead to significantly higher global oxygen delivery, reducing the number of low-delivery areas by 50%, with maximum effect in oligemic areas (highest risk of ischemia), without

affecting the $CMRO_2$. Also, the resultant increase in blood viscosity, secondary to RBCT, did not decrease cerebral blood flow significantly, a main concern in previous studies, as loss of autoregulation did not allow normal vasoconstriction, in response to a higher arterial content of oxygen. Importantly, transfusion was also able to reduce the oxygen extraction fraction (OEF), raised in the context of anemia, thus increasing cerebrovascular reserve, and the brain's resistance to additional ischemic injury [74].

Some authors have proposed that blood viscosity should be a transfusion trigger [75]. In fact, anemia leads to low blood viscosity, to which the microvascular system responds through vasoconstriction, with decrease of blood flow and in the percentage of open capillaries, resulting in lower functional capillary density (FCD). RBCT can help in the normalization of FCD through 2 mechanisms: by raising blood viscosity, resulting increase in shear stress results in the releasing of vasodilating substances from the micro-vessels, such as nitric oxide and ATP [76]; by raising hemoglobin concentrations, this molecule functions as oxygen sensor, leading to additional releasing of the same vasodilating substances, consequently raising blood flow and oxygen delivery [20].

Finally, other factors, such as age and gender, should also been taken in account. Arellano-Orden *et al.* have shown that women and younger individuals victims of severe TBI, have significantly higher increments in $P_{bt}O_2$ after transfusion of red blood cells [77].

(2) What is the effect of RBCT on the brain's metabolism?

Cerebral microdyalisate studies have mostly shown that, although red blood transfusions improve brain oxygenation, they appear to have little to no effect in the brain's metabolism. Has mentioned previously, lactate:pyruvate ratios (LPR) can be measured in the cerebrospinal fluid, and compared to assess the effects of RBCT, with values over 25 being indicative of tissue ischemia.

Zygun *et al.*, in a clinical study of 30 severe TBI patients [65], observed a increase of LPR in 56% of individuals, and no significant change in cerebral pH. Also, no significant correlation was found between hemoglobin concentrations' and LPR's variations (p = 0,76), but posterior analysis revealed a significant association between these two variables and the prediction of $P_{bt}O_2$ change (p = 0,023). If baseline LPR was under 25, there was no significant association, but, for patients with higher exposure time to anoxia (baseline LPR above 25), an increase of 1 g/dL of Hb concentrations was associated with a significant increase of 0,18 kPa of $P_{bt}O_2$. This 2009 study was the first to study the effects of RBCT in cerebral metabolic markers, and found no benefits of RBCT to the brain's metabolism [65]. Another more recent study into SAH patients [78] also demonstrated no significant changes in LPR after RBCT, and no significant association between variations of Hb concentrations and LPR.

Unfortunately, no studies of this nature have yet to be conducted in TBI patients.

(3) Does the storage age of RBC's influence the effects of this therapy?

In recent years, concern been raised about the effect of the storage age of red blood cells on their oxygen-transporting ability, and the irreversible changes that occur during storage and how they affect clinical outcomes in transfused patients.

First of all, RBC's can be stored in liquid mediums for up to a maximum period of 35 to 42 days, with a mean age of 2-4 weeks for units transfused in the ICU [39]. The so-called "storage lesion" includes a diversity of physical and metabolic irreversible changes, whose magnitude increases with longer storage times, including [79]:

- lower pH, with resulting acidosis, which endangers the survival and metabolic pathways of red blood cells;
- reduction of ATP, due to blockage of glycolysis, with less energy available for the cell's metabolism;

- reduction of 2,3-DPG (2,3-diphosphoglycerate) concentrations, with less NADH (nicotinamide adenine dinucleotide reducing equivalents) production, lower met-hemoglobin reductase activity and, consequently, higher concentrations of met-hemoglobin (biologically inactive), jeopardizing the RBC's oxygen delivery capacity;
- accumulation of extra-cellular potassium, with higher risk of potentially lethal arrhythmias;
- membrane loss, with concomitant increase of plasma-free hemoglobin, which binds to endothelial nitric oxide, inducing inappropriate vasoconstriction;
- membrane deformities, which may compromise microvascular circulation and elevate the risk for microthrombosis;
- oxidative injury to membrane proteins, decreasing the integrity of the cell's cytoskeleton and creating neo-antigens;
- oxidative injury to phospholipids with formation of biologically active metabolites, increasing the risk of TRALI;
- loss of carbohydrates from the membrane leads to the increase of cell adhesion to the vessel's wall;
- bacterial contamination, which can cause septic shock.

Also, leucocytes, which are stored with red blood cells in whole blood, produce cytokines and other pro-inflammatory substances that can potentiate the RBC's storage damage, such as an increase in cell adhesion to the vascular endothelium [80]. These immunomodulatory mechanisms are less well understood, but still have led to recommending universal leukoreduction, in order to reduce transfusion-related complications, with controversial results [81,82].

In order to understand the effect of storage age of RBC's in critical care, and specifically in traumatic brain injury patients, several studies have been conducted, with controversial

results. It was, firstly, hypothesized that "fresher than usual" blood, compared to the standard of 20-25 days of storage age, would present less storage lesion and, therefore, lead to fewer complications.

The ABLE trial (Age of Transfused Blood in Critically Ill Patients) [83], a multicenter, randomized, blinded trial, conducted in 64 centers in Canada and Europe, studied the effects of "standard" versus "fresher" red blood cell units in 2413 patients, randomly allocated to one of the treatment arms. They concluded that there was no benefit in transfusing "fresher than usual" RBC's, as both primary outcomes (90-day all-cause mortality) and secondary outcomes (organ dysfunction, infection rates, length of stay in ICU and hospital settings, duration of organic support, adverse events and transfusion reactions) were similar in both groups. These results were consistent with the results from other previous clinical trials ([84,85]), and were not consistent with older observational studies that associated longer age of storage of RBC's to harmful effects ([80,86,87]).

In TBI, Yamal *et al.* showed no significant differences in brain oxygenation, long-term neurologic deficits and mortality between 200 severe TBI patients randomly assigned to receive "older"(≥ 14 days) versus "younger" (<14 days) RBC units [66], and Weinberg *et al.*, in a trial of 1647 trauma patients, determined that the age of RBC units was not associated to a higher mortality risk [88].

Therefore, we can conclude that RBC units with age storage shorter than standard recommendations does not present significant benefits for critical care patients, including TBI patients, and that blood banks should follow the same recommendations for transfusion of critically ill patients in TBI cases, according to the age of storage.

(4) What is the effect of RBCT in clinical outcomes in TBI patients?

Besides mortality, neurological outcome scores are one of the main short and long-term outcome measures assessed in traumatic brain injury patients, as TBI is one of the major causes of long-term disability worldwide [89].

Patients who suffer TBI are more prone to develop permanent disabilities, with 35% of the survivors suffering from significant long-term neurological deficits [8], and 52% living with moderate to severe disabilities after a 1-year follow-up [90].

In order to assess long-term neurological outcomes in TBI patients, multiple scales have developed and widely used [91], the main being: the Glasgow Outcome Scale (GOS) [92], the Rancho Los Amigos Levels of Cognitive Functioning Scale (RLCFS)[93], and the Disability Rating Scale (DRS) [94].

Leal-Noval *et al.*, in a 3-year prospective study of RBCT's association with neurological outcomes scores, in 309 TBI patients admitted to the neurological intensive care unit [95], used these three scales to evaluate neurocognitive and disability levels at a 1 year follow-up, and concluded that patients who received blood transfusions (53% of the study's population) had significantly higher rates of unfavorable neurological scores at 6- and 12-months follow-up. This patient subgroup also a presented significantly longer stay in neurocritical care units, and a higher hospital mortality rate ($p < 0.01$). Although this study's results contradicted the findings from previous studies ([96,97]), it provided valuable information due to its strengths, as being the largest study to date to investigate this association, and the first to apply different statistical methods in analyzing the same association.

Based on these conclusions, the authors advised practicians and intensivists to exert caution when giving RBCT's in TBI patients, due to the study's limitations.

Previous to the publication of the TRICC trial (Transfusion Requirements in Critical

Care) in 1999, the common practice was that red blood cell transfusion (RBCT) was recommended for general care and ICU patients who were diagnosed with anemia and whom hemoglobin concentrations were lower than 10 g/dL [98]. This "liberal" approach was compared to a more conservative / "restrictive" approach (only performing RBCT if hemoglobin concentrations lower than 7 g/dL) in the TRICC trial, by randomizing 838 critically ill patients with isovolemic anemia [25].

The results of this trial included:

- The base-line characteristics were similar between the two treatment groups;
- Patients who were not enrolled, due to exclusion criteria, refusal to consent or withdraw from the trial, were slightly older ($p = 0.04$) and had a lower percentage of cardiac disease ($p < 0.01$) as their primary diagnoses, but there were no significant differences in the remaining primary diagnoses ($p = 0.26$) nor in the disease severity (APACHE II scores were similar, $p = 0.36$).
- Patients randomized for the restrictive-strategy group, due to the lower threshold used, had relatively less 54 percent transfusions, and 33 percent did not receive any transfusion, while every patient in the liberal-strategy group received at least one unit of RBC during the trial.
- There were no differences in the primary outcome, which was the rate of death from all causes in the first 30 days after admission, and mortality during hospitalization (compared to mortality at 60 days or in the ICU) was actually significantly lower in the restrictive group.
- During subgroup analyses, two groups stood out from the others, due to a significantly lower mortality in the restrictive strategy patients: patients younger than 55 years ($p = 0.03$), and patients with a lower disease severity (APACHE II score ≤ 20 points, $p = 0.02$).

- After adjustment for possible confounders, multiple organ-dysfunction scores were significantly higher in the liberal-strategy group ($p = 0.03$), and, compared to the baseline score, changes in these scores were significantly higher in the same group ($p = 0.04$). The liberal group also experienced a significantly higher percentage of cardiac complications ($p < 0.01$), specifically myocardial infarction ($p = 0.02$) and pulmonary edema ($p < 0.01$).

Thanks to the results of the TRICC trial, red blood cell transfusion practices changed forever in both the general and intensive care units. Although previous similar trials and studies had been conducted on this subject ([26,99–102]), the populations studied in these trials were rather small or too specific, making it difficult to generalize results for the majority of critically ill patients.

Therefore, it is safe to recommend the use of an hemoglobin concentration threshold as low as 7.0 g/dL in ICU units, while maintaining such concentrations in a range of 7.0 to 9.0 g/dL, as this strategy is at least as effective and possibly superior to a more liberal transfusion strategy (with a threshold of 10.0 g/dL, and a maintenance range of 10.0 to 12.0 g/dL) [25].

At the time, no large randomized controlled trial had been conducted in the traumatic brain injury population, reason why clinicians and intensivists were still fearsome and cautious in the application of this findings in this type of patients.

Since then, various studies have analyzed the effects of this restrictive strategy in TBI patients.

Several retrospective studies [61,103,104] have shown that RCBT was not associated with worse outcomes in TBI patients, compared with patients who did not receive transfusions. Salim *et al.* [60] conducted a retrospective study on blunt trauma patients with TBI, in which

both anemia and blood transfusion, when analyzed separately, were associated to a higher mortality and complications' risk, but when this two patient's characteristics were combined, RBCT was associated to worse outcomes, but anemia was not. Duane *et al.* [105], in their own retrospective review of 788 TBI patients, also associated blood transfusions with worse outcomes, but believe there is a dose-dependent effect, as non-survivors had received higher numbers of blood products, although they also considered the need to transfuse, due to the patient's critical condition, a confounder between mortality factors.

The ABC (Anemia and Blood Transfusion in Critically Ill Patients)[106], and SOAP (Sepsis Occurrence in Acutely Ill Patients)[96] trials, conducted in adult ICU patients, showed similar results to the TRICC trial, with no significant association found between RBCT and worse outcomes. McIntyre *et al.* [107], in a subgroup analysis of the TRICC trial conducted in 2006, studied 67 patients with TBI, and found no significant differences between the restrictive and liberal threshold groups, in terms of 30-day mortality (p = 0,64), ICU (p = 0,26) and hospital length of stay (p = 0,72), and multi-organic dysfunction (p = 0,35). A randomized clinical trial on the effects of erythropoietin (EPO) and two different transfusion thresholds (7 and 10 g/dL) [108], performed in 200 closed head injury patients, showed no interaction between EPO and hemoglobin thresholds, no benefit in EPO treatment, and a higher adverse events rate in the 10 g/dL threshold group, mainly thromboembolic events. Therefore, no evidence was found to support a liberal approach to transfusion.

Studies done in critical pediatric care populations have also shown little benefit in liberal transfusion strategies. In the TRIPICU (Transfusion Requirements in the Pediatric Intensive Care Unit) trial, 637 stable, but critically ill children, presenting anemia (Hb <

9,5 g/dL) in the first seven days within admission, were randomly assigned a restrictive or liberal transfusion threshold (7 g/dL, or 9,5 g/dL, respectively). Children in the restrictive group received 44% fewer transfusions, with 54% receiving no transfusion at all, compared with only 2% of the children in the liberal group. No significant differences in multi-organ dysfunction, mortality and other adverse outcomes were found, between the two groups, rendering restrictive transfusion practices safe for pediatric ICU patients. The same was verified in a latter subgroup analysis of 66 children that suffered any form of brain injury [109]. In opposition, Bell *et al.* conducted a randomized clinical trial comparing two different transfusion thresholds based on hematocrit levels (restrictive versus liberal methods), enrolling 100 preterm infants. Infants in the restrictive group received less transfusions, but had more adverse side effects, mainly intraparenchymal brain hemorrhage, periventricular leukomalacia and more frequent episodes of apnea (both mild and severe), making the restrictive approach to RBCT not suitable for preterm infants [110]. Another trial, conducted in 441 extremely low birth weight infants (<1000 grams), comparing low and high hemoglobin thresholds for transfusion, found that, although infants in the low threshold group received significantly fewer transfusions (p = 0,037), outcomes were similar, showing little to no benefit in maintaining higher levels of hemoglobin concentration [111].

In order to understand how clinicians apply guidelines and evidence-based recommendations in their day-to-day practice, two surveys were performed in North America. More than half of the practicians questioned responded to the surveys. One survey's purpose [112] was to determine the hemoglobin threshold used by doctors from 3 different specialties, in 2 different clinical scenarios of TBI, where one presented with intracranial hypertension, and the other did not. Depending on specialties, variability in used thresholds was observed, with neurosurgeons using higher mean thresholds,

independently of intracranial pressure, being less considering of the immunodulatory effects of RBCT, and relying less in indicators of anemia intolerance. Apart from these disparities, all groups believed that secondary ischemic injury was a main concern after TBI. The other survey [113] assessed common triggers used by practicians in the administration of blood transfusions in SAH patients. Once again, variability in responses was significant, with more liberal goals of hemoglobin concentrations for patients with high-grade SAH or delayed cerebral ischemia (DCI), while restrictive thresholds were preferred in low-grade SAH. Neurosurgeons continue to prefer higher minimum Hb levels, and transfusion of more RBC units, when compared to intensivists. The existence of protocols based in guidelines was associated to more restrictive thresholds, advanced seniority was correlated to higher Hb goals, and practicians were more comfortable with transfusing patients if they presented objective signs of cerebral ischemia ($P_{bt}O_2$ < 15 mmHg, and LPR > 40).

Reviews on transfusion practices in acute brain injury highlight the clinical equipoise affecting this theme, as evidence is, sometimes, contradictory. It is still essential to determine if anemia and the need to transfuse are consequences of the disease itself, or independent indicators of outcome [3]. Also, although restrictive transfusion thresholds have been objectively considered as safe as liberal methods, practicians still consider TBI patients to be particularly sensitive to anemia, reason why more liberal thresholds are, in real life clinical scenarios, implemented in these patients, especially in symptomatic anemia [114].

CURRENT GUIDELINES

When analyzing the multiple guidelines who handle the treatment and management of ICU patients and specifically neurocritically ill patients, including TBI patients, there is a lack of strong evidence-supported recommendations and even, at times, a complete absence of red blood cell transfusion referral as a mean of treating these patients.

The American Heart Association/American Stroke Association (AHA/ASA) guidelines include a recommendation for the use of packed red blood cell transfusion (RBCT) for treating anemic patients who are at risk of cerebral ischemia, in case they suffer from aneurysmal subarachnoid hemorrhage (aSAH) [115], but the optimal hemoglobin goal is not defined, due to the lack of evidence (class IIb, level B). Although those guidelines were published 2012 and may be, therefore, outdated, they are still more informative than the guidelines for spontaneous intracerebral hemorrhage (ICH) [116] or acute ischemic stroke (AIS) [117], which were published in 2015 and 2018, respectively, and do not make any reference to RBCT. The same occurs with Traumatic Brain Injury, where even the most recent guidelines from the Brain Trauma Foundation [44], published in 2016, do not included RBCT in their treatment plan.

The American Academy of Neurology (ANN) has published guidelines informing practicians how to handle specific situations related to TBI, as antiepileptic drug prophylaxis [118] and reducing brain injury after cardiopulmonary resuscitation [119], but not about TBI itself or the role of RBCT in these patients.

The Congress of Neurological Surgeons (CNS) did publish guidelines about the acute medical treatment of TBI, but only specifically for pediatric patients, without making any reference to RBCT [120].

Although this two specialists' societies have not directly published guidelines referring to red blood cell transfusion as a treatment tool for TBI patients, they have, conjointly with the American Association of Neurological Surgeons (AANS), taken part in the

development of other neurological pathological entities' guidelines, including the Brain Trauma Foundation's Guidelines for TBI, which, as referred previously, does not handle the subject of RBCT in this patient subgroup.

On the other hand, societies more related to blood transfusions themselves and treatment of ICU patients have published guidelines and articles about the thresholds that should be used when transfusing TBI patients. The American Society of Anesthesiologists (ASA) defends a restrictive strategy for red blood cell transfusion in all patients, if hemoglobin levels are lower than 8 g/dL and hematocrit is lower than 25%, arguing that RCT's done on the issue show similar length of hospital stay, mortality and complication rates, and a lower need of transfusions (according to meta-analysys of RCT's), when compared to the previously advocated liberal strategy [121]. The American Association of Blood Banks (AABB) equally recommends a restrictive RCBT threshold in which transfusion should be given to hospitalized adult patients (including ICU patients) who suffer from anemia and whose hemoglobin levels are under 7 g/dL, excluding patients who have been diagnosed with acute coronary syndrome, severe thrombocytopenia or chronic transfusion-dependent anemia. However, a threshold of 8 g/dL should be considered for patients who have preexisting cardiovascular disease, or are undergoing orthopedic or cardiac surgery. Also, RBC units should not be limited to fresh blood, any age of storage can be selected, as long as it is within the licensed dating period [122].

Also, the American College of Surgeons Trauma Quality Improvement Program (ACS TQIP) published a "best practices" guideline for TBI management, in which they highlight the importance of closely monitoring anemia and coagulopathy, as they are commom in TBI patients. The restrictive strategy for transfusion (Hb threshold of 7g/dL) is recommend, based on recent randomized clinical trial's results, which, as in the TRICC trial, showed no significant differences in neurological outcomes, and a higher percentage of adverse outcomes in the liberal strategy, when comparing the two treatment methods.

Nowadays, the most complete guidelines about the treatment of anemia in critically ill patients are provided by the British Committee for Standards in Haematology [39]. They make evidence-based recommendations for each subtype of brain injury, for other diverse clinical entities that may require blood transfusions, but also tackle ways of reducing transfusion requirements and how to treat specific complications of transfusion. **Table 1** (see in Supplementary Material) resumes the recommendations for patients in neurocritical care.

Ongoing Studies

There are two ongoing randomized trials being conducted on the optimal transfusion threshold for TBI patients: the Transfusion Strategies in Acute Brain Injured Patients/TRAIN trial (NCT02968654), and the Hemoglobin Transfusion Threshold in Traumatic Brain Injury Optimization/HEMOTION trial (NCT03260478).

The TRAIN trial (2016-2021) is a prospective, multicenter, randomized, pragmatic trial, that will enroll 4610 participants suffering from acute brain injury (including TBI, SAH and ICH patients), and randomly assigned them to either a restrictive or liberal transfusion threshold (<7 g/dL, and <9 g/dL, respectively). The primary outcome will be a good neurological outcome at 180 days after randomization, defined by an extended Glasgow Outcome Score (eGOS) of 6-8, while secondary outcomes will include various variables, including survival, changes in Glasgow Coma Score (GCS), ICU and hospital length of stay, multi-organic dysfunction, infection rate, brain oxygen pressure ($P_{bt}O_2$), and serious adverse events to transfusion.

At the same time, the HEMOTION trial (2017-2021) will enroll less patients (712), but will exclusively enroll severe blunt TBI patients, with GCS ≤ 12 points and anemia (defined as Hb ≤ 10 g/dL). These patients will, as in the previous trial, be randomly assigned a restrictive or liberal transfusion threshold (in this case, ≤ 70 g/L, and ≤ 100 g/L, respectively). The primary outcome will be the same as in the TRAIN trial, with secondary outcomes including mortality at 6 months, patient function, overall and TBI-specific quality of life, depression, return to day life activities, and transfusion-related complications.

We hope the results from these trials will contribute to enlarge the quality of evidence about the effects of transfusion in TBI patients, and to strengthen recommendations for transfusion practices in these patients.

Daily Practice Considerations

As both anemia and blood transfusion have been both inconsistently associated with worse outcomes in TBI, and the effects of RBCT in brain oxygenation are controversial, a "blood transfusion anemia paradox" has been the cornerstone for lack of high-quality evidence-based recommendations in managing anemia in TBI patients.

In light of all the evidence available about the use of different transfusion triggers in acute neurologic pathological states, a recent review [123] has developed a "practical approach" for treating anemia in ABI, that can be extrapolated for TBI patients.

Through complete neurological examination, patients should be immediately classified in awake-conscious or poor-grade individuals, based in neurological findings/deficits and neurologic status classification scores, e.g., a Glasgow Coma Scale (GCS) score lower than 8 points (coma) should be considered a poor-grade status.

After that, and according with the recommendations for general ICU patients, patients with brain injury and a good neurological status should be submitted to "restrictive" transfusion practices and repeated clinical surveillance, in order to assess immediate and short-term effects of transfusion, including adverse effects, as well as treatment of other potentially life-threating conditions.

In case of patients with baseline poor neurological status or with rapid deterioration of such, the decision to transfuse should be individualized and based in both "systemic" and "cerebral" triggers.

"Systemic" triggers should focus on the mixed or superior venous cava oxygen saturation (SvO_2 or $ScvO_2$) and blood lactate levels. SvO_2 or $ScvO_2 > 70\%$ is considered a marker of oxygen delivery optimization, and can be achieved through various treatments, from positive pressure ventilation to RBCT, as shown in the SOAP trial [96]. Also, is has been demonstrated that achieving an $ScvO_2 > 65\%$ after anoxic brain damage can reduce mortality [124] and improve neurological outcomes [125]. Normalizing systemic lactate levels

is also one the goals of intensive care practicians [126], as lactic acidosis is a marker of tissue ischemia and hypoperfusion, and, as other acid-base abnormalities, is associated to a higher risk of multi-organic dysfunction and death [127]. RBCT should, therefore, only be considered if these "systemic" markers of tissue hypoxia are abnormal.

"Cerebral" triggers, on the other hand, refer to brain oxygenation markers, such as $P_{bt}O_2$, rSO_2 and jugular venous saturation ($SjvO_2$). Patients with $P_{bt}O_2$ < 15-20 mmHg and $SjvO_2$ < 55% are at high-risk of secondary brain damage, as these are indicators of cerebral hypoxia[51], which can be caused either by low systemic oxygen delivery or, in the case of normal DO_2, due to other causes of cerebral hypoperfusion.

Practicians should, firstly, guarantee a good systemic vascular support for oxygen delivery to the brain, by treating systemic infirmities (such as systemic hypotension, hypoxemia, hyperthermia), and, if low cerebral perfusion remains a concern, rule out organ-specific causes for this issue (such as severe hypocapnia or intracranial hypertension). In this case, RBCT can be considered in patients with normal DO_2 and cerebral hypoxia signs, and should always be considered in patients with low systemic and cerebral oxygen delivery.

The choice to transfuse in TBI patients continues to represent a clinical challenge for intensivists, even in the presence of highly advanced neuromonitoring tools and technological resources for treating systemic maladies.

Conclusion

The lack of consistency in data related to anemia, blood transfusions and their effects in traumatic brain injury patients, cannot allow practicians to create safe and strong evidence-based protocols for the treatment of such patients, and do not permit the establishment of specific transfusion triggers in common practice.

While we await the results from RCT's and other studies dealing with the issue, red blood cell transfusions, as in all other blood products, should be carried out in an individualized and precautious manner, taking in account various variables indicative of the patient's status.

More randomized controlled trials, with bigger populations, should be a major priority in intensive care, in order to unravel the present imprecisions in this issue.

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Conflicts of interest

No conflicts of interest to declare.

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Supplementary Material

Table 1: Target hemoglobin values for patients with acute neurologic injury. TBI, Traumatic Brain Injury; AIS, Acute Ischemic Stroke; SAH, Subarachnoid Hemorrhage; ICU, Intensive Care Unit

7-9 g/dL	> 9 g/dL	8-10 g/dL
• TBI	• TBI and evidence of cerebral ischemia • AIS (in ICU)	• SAH

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